PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
MIC-001 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/02180	14/04/1998	14/04/1997
International Patent Classification (IPC) or national classification and IPC		
C07K16/00		
Applicant		
MICROMET GESELLSCHAFT FÜR BIOMEDIZINISCHE...		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 51 sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
VI	☐	Certain documents cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/11/1998	08. 12. 99
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hoesel, H Telephone No. +49 89 2399 8693

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Int mational application No. PCT/EP98/02180

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-42	as originally filed			

Claims, No.:

1-33	as received on	23/08/1999	with letter of	23/08/1999

Drawings, sheets:

1/20-20/20	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	9, 11 - 16, 21, 22, 26 - 32
	No:	Claims	1 - 8, 10, 17 - 20, 23 - 25, 33
Inventive step (IS)	Yes:	Claims	11 - 13, 21, 22, 28 - 32
	No:	Claims	1 - 10, 14 - 20, 23 - 27, 33
Industrial applicability (IA)	Yes:	Claims	1 - 33
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether th claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1: A. HOESS ET AL., Proc. Am. Ass. Cancer Res. vol. 38, March 1997, p. 30
D2: WO-A-97/00271
D3: WO-A-93/11236

SECTION I:

1. Sequence listing pages 1 - 46, filed with the letter of 08.09.99, are also included as the basis for the present report.

SECTION V:

2.1 The claimed method of recombinantly producing human antibodies or fragments directed against human antigens is characterized in the use of Ig genes of unprimed mature B-cells for establishment of a cDNA library. The applicant considers the subject-matter to be limited with respect to closest prior art of D3 since the use of Ig genes obtained from anergic cells has been deleted from the claims. According to the applicant's arguments antibodies derived by this method contain heavy chain germ-line V_H-segments without any somatic mutations.

2.2. It is known that mature, unprimed as well as primed, anergic B-cells express membrane bound IgD and IgM. The applicant pointed out that also primed memory B-cells express surface IgM and IgD.

2.3. Methodology as actually disclosed:
According to the description and e.g. claim 4, the present method relies establishment of a gene library by amplification of rearranged IgD heavy chains. Thereby, however, **all possible surface expressed germ-line or matured IgD heavy chain sequences** will be included in the library, whether they originate from unprimed mature, primed, anergic or primed memory B-cells. The description does not mention any further procedural step that allows separation of unprimed from primed B-cells. Interpretation of the claim 1 as to encompass the use of Ig V_H segments originating from mature, unprimed B-cells only is thus, i.e. inconsistent with the actual disclosure, contrary to Art. 6 PCT (cf. description p. 7, 1st

paragraph and the paragraph extending between p. 7 and 8, p. 16, 2nd paragraph)..

2.4. Disclosure of Document D3:
D3 concerns methods to recombinantly produce human antibodies directed against human antigens. In this document, the potential suitability of unprimed B-cells (or anergic ones) for establishment of phage display libraries is emphasized. Gene libraries for phage display have been prepared by reverse amplification of IgM heavy chain sequences from peripheral blood lymphocytes. Thereby rearranged heavy chain variable sequences of (i) mature unprimed and (ii) primed B-cells have been amplified.

Moreover, D3 explicitly points to the advantages associated with the specific **amplification of IgD sequence** in order to produce a library of genes enriched for **"naive, unselected V-gene sequences"** (D3, p. 16, lines 19 - p. 17, line 5, particularly p. 16, lines 35 and 36 and p. 7, lines 34 -38) and discloses the amplification of IgD mRNA by means of specific primers as an alternative. Necessarily, these rearranged IgD sequences are derived from mature, unprimed B-cells (as well as primed, anergic and memory B-cells) and thus have been subject of in vivo selection to eliminate self-aggressive reactivities. This alternative method of D3 is identical with that set forth in the present application.

Consequently, D3 is considered to anticipate the method according to present claims 1 - 7, 10 and 17.

It is noted that even when using Ig gene libraries resulting from amplification of IgM V_H genes, also germ line V_H sequences will be obtained to a certain degree of probability, because mature, unprimed B-cells express surface bound IgM.

3. Claims 18 to 20:

3.1. The applicant considers the antibodies obtained by the present method to be novel with respect to those of D3 as they contain Ig heavy chains containing the germ-line V_H segments without any somatic mutations. In this connection, additional evidence for the presence of nucleotide changes in the gene sequences

of the antibodies disclosed in D3 with respect to their closest germ line sequences has been submitted.

3.2. Scope of the said claims:

Claim 18 does not contain a structural definition of the desired anti-human antibody. These are functionally defined and in terms of the method of production.

The scope of claim 18 is obscured by the use of relative terms such as "**low** immunogenic" and especially by the wording "**essentially** unprimed". It appears that a B-cell is either primed or it is not. When interpreting the above term as to extend to "**not unprimed**" B-cells, human antibodies having rearranged and mutated heavy chains are covered by the scope of claim 18. As discussed above, the method as actually disclosed allows the production of a manifold population of antibodies including those which have somatically matured Ig V_H segments. containing either the unchanged germ-line sequence or one having somatic mutations (in the case of anergic or memory B-cells).

It is noted that according to the additional evidence (annex 2) further "artificial" recombinations may be introduced by PCR. Consequently, antibodies containing those artificially recombined Ig V_H segments do not longer express a particular, unchanged germ-line V_H gene sequence.

In this instance, the claims 18 to 19 (20) extend to any (tumour antigen specific) recombinant human-anti-human antibody such as disclosed in any of D1 - D3 and thus lack novelty, contrary to Art. 33(2) PCT.

3.3. Even if interpreting claim 18 in the narrower sense, it lacks novelty with respect to D3. The methods disclosed therein permit the amplification and expression of Ig heavy chains from mature, unprimed B-cells in a combinatorial library and their use for the production of recombinant human antibody (fragments). These will exhibit the desired sequence identity. In connection with the evidence submitted it is noted that the nucleotide changes shown to be present in the Ig V_H gene sequences of Muc-1 and TNF-E7 are conservative ones (ACA to ACG for TNF-E7; GGG to GGA, TCC to TCT and TTC to TTT for Muc -1), i.e. are not expressed

at the amino acid level. Consequently, the antibodies themselves cannot be structurally distinguished from those derived from an unprimed, mature B-cell.

It follows from the above that (i) the latter two antibodies are detrimental to the novelty of claims 18 to 20 and (ii) that antibodies having Ig V_H segments from mature B-cells cannot necessarily be distinguished from others containing Ig V_H segments originating from primed, anergic B-cells, if the somatic mutations do not effect at the amino acid level.

3.4. The objections set out under 3.2 and 3.3 analogously apply to claim 33 insofar as referring to claim 18.

4. The disclosure of D3 extends to kits for carrying out the disclosed phage display system (claims 18 and 19). As the combination of particularly suitable reagents into such a kit is obvious, the subject-matter of claims 26 and 27 does not meet the requirements of Art. 33(3) PCT in view of D3.

5. It appears that claims 14 - 16 extends to conventional modifications of obtaining functional, complete antibodies suitable for therapy. These features do not appear to confer inventive step when incorporated into the independent claims (Art. 33(3) PCT.

6. Claims 8 and 9 try to define the method in terms of a result to be achieved, i.e. the antibody to be obtained. This feature is in the present case irrelevant for characterizing the method as such and as limitation with respect to the prior art. It is thus is not suitable to confer novelty or inventive step.

7. The modifications according to claims 11 - 13 appear not to be derivable from any of D2 and D4. As the particular features allow to increase the probability to retrieve antibodies of desirable specificity and affinity characteristics, the said claims are considered to contain novel and inventive subject-matter.

8. With respect to the limitation, the receptor according to claim 21 and 22 appears to be novel and inventive in view of the closest prior art of D1 (Art. 33(2) and (3) PCT.

9. Claims 23 - 25 do not meet the requirement of Art. 33(2) and (3) PCT:

9.1. The said claims are broadly directed to the entire Ig V_H/V_L chain of a receptor according to claims 18 - 20 or CDRs (CDR3) derived therefrom. Although it is argued that the said portions contribute to the low immunotolerance, no particular structural motifs have been correlated with the alleged functional characteristics. Consequently, the claims extends to any human Ig V_H or V_L chain (which in the present method may originate from any potential B-cell irrespective whether it is immature, mature or primed) or CDRs derived therefrom. As set out above, claim 18 is in no way limited to e.g. unprocessed Ig V_H or e.g. IgD chains.

9.2. Recombinant antibodies falling within the terms of claim 18 have been described in at least document D3 (see item 2.3). When considering claim 18 in broader terms (see item 3.2), also documents D1 and D2 disclose subject-matter falling within the claims. Isolated human V_H or V_L chains have been described in various instances in the prior art and are necessarily obtained by following the procedural steps given in D3. Consequently, the subject-matter of claims 23 and 24 lacks novelty, contrary to Art. 33(3) PCT.

9.3. Although it may be agreed that CDR's form an essential part of the immunogenic profile of an antibody, it may not be ignored that its conformation of a CDR is significantly effected on by the environment given by the framework and the other CDR's forming the epitope binding region. It appears furthermore that, an observed low immunogenicity of a CDR is dependent on its actual conformation and thus the environment by which it is presented rather than its sole primary sequence. Likewise the technical effect of obtaining **immunoglobulins directed against human antigens of low immunogenicity** is not associated with the discovery of particular isolated CDR sequences, but in **the particular coordination of the six CDRs** per epitope binding region and **with the respective tolerated sequences of framework and constant regions.**

Thus, even if distinguished from known sequences so as to be novel, no particular advantageous effect can be contributed for isolated CDRs as covered by any of claims 23 - 25. Any CDR isolated by the present method represents equivalents to known CDRs and thus lack inventive step, contrary to Art. 33(3) PCT (see also

section VIII).

The objection analogously applies to claim 32, insofar as referring to claims 23 - 25.

SECTION VII:

10. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2 and D3 is not mentioned in the description, nor are these documents identified therein.

SECTION VIII:

11. According to the applicant's arguments, the low immunogenicity of the present human anti-self antibodies is due to the presence of at least an Ig V_H chain exhibiting the **V_H germ line sequence** (originating from mature unprimed B-cells that have not eliminated after activation by self antigens and subsequent clonal selection). This structural feature is therefore essential for the technical problem to be solved and thus should be included in claim 28 for reason of Art. 6 PCT.

12. The meaning of the wording "**essentially** unprimed" is not clear and renders the scope of claims 1 and 18 obscure (see section V).

23. AUG. 1999

CLAIMS

1. A method for the production of an anti-human antigen receptor that is low or not immunogenic in humans comprising the steps of selecting a combination of functionally rearranged VH and VL immunoglobulin chains wherein at least said VH chain is derived from essentially unprimed mature human B-lymphocytes ~~or from essentially anergic human B cells~~ and said VL chain is derived from a naturally occurring human B cell repertoire, said chains being expressed from a recombinant vector and using an in vitro display system for binding to a human antigen.

2. The method according to claim 1 wherein said receptor is an immunoglobulin or a fragment thereof.

3. The method according to claim 2 wherein said immunoglobulin fragment is a Fv-fragment.

4. The method according to any one of claims 1 to 3 wherein at least said VH and optionally said VL immunoglobulin chains are derived from a human IgD repertoire.

5. The method according to any one of claims 1 to 4 wherein said in vitro display system is a phage display system.

6. The method according to any one of claims 1 to 5 wherein said combination of rearranged chains is expressed from one or more different libraries.

7. The method according to any one of claims 1 to 6 wherein said human antigen is a tumor antigen.

8. The method according to claim 7 wherein said tumor antigen is the human 17-1A antigen.

9. The method according to claim 8 wherein said VH-chain comprises one of the two sequences shown in Fig. 7 (nucleotides 1 to 381) and Fig. 8 (nucleotides 1 to 339) and/or said VL chain comprises one of the two sequences shown in Fig. 6 (nucleotides 1 to 321) and Fig. 9 (nucleotides 1 to 321).

10. The method according to any one of claims 1 to 9 wherein said selection step involves

(i) binding of the display vehicle expressing an antigen receptor

(a) on immobilized target antigen or fragments thereof;

(b) on optionally labeled cells expressing the target antigen or fragments thereof;

(c) or to soluble, preferably labeled target antigen or fragments thereof;

(ii) washing off non-specifically binding display vehicle (a and b) and subsequent elution of specifically binding display vehicle

or

(iii) positive enrichment of target antigen bound display vehicle (b and c) from target antigen solution or from suspensions of cells expressing the target antigen;

thus isolated display vehicles including their antigen receptors optionally being multiplied by replication and subjected to further rounds of in vitro selection as described in (i) to (iii).

11. The method according to any one of claims 1 to 10 wherein prior to said selection step either said VH or said VL chain is selected for binding to said antigen together with a surrogate V chain.

12. The method according to claim 11 wherein said surrogate chain is a mouse VH or VL chain.

13. The method according to any one of claims 1 to 12 wherein said selection of a suitable combination involves

(a) testing one and the same VH chain in combination with a variety of different VL chains for binding to said human antigen; or

(b) testing one and the same VL chain in combination with a variety of different VH chains for binding to said human antigen.

14. The method according to any one of claims 1 to 13 further comprising the steps of obtaining, after selection, the human VH and VL chains or the corresponding nucleic acids and fusing said chains to the same or other VH or VL chains, to immunoglobulin constant regions of heavy (CH) or light chains (CL) or parts thereof or to non-immunoglobulin chains and the corresponding nucleic acids, respectively.

15. The method according to claim 14 wherein said constant region chains are derived from human IgG1 or IgG3.

16. The method according to any one of claims 1 to 13 further comprising the steps of obtaining, after selection, the human VH and VL chains and physically linking said chains to non-proteinous pharmaceuticals and/or other biologically active molecules.

17. The method according to any one of claims 1 to 16 wherein said VH or VL chains are expressed from nucleic acid sequences that are the result of the RT-PCR amplification of mRNA derived from essentially unprimed mature human B-lymphocytes or from essentially anergic human B-cells.

18. An anti-human antigen receptor that is low or not immunogenic in humans, comprising a combination of functionally rearranged VH and VL chains ~~[preferably]~~ from essentially unprimed mature human B-lymphocytes ~~[or from essentially anergic human B-cells]~~ and said VL chain obtainable by the method according to any one of claims 1 to 17.

19. The receptor according to claims 18 which is an antibody or a fragment thereof.

AMENDED SHEET

wherein at least said VH chain is derived

is derived from a naturally occurring human B cell repertoire, said anti-human antigen receptor being

20. The receptor according to claim 18 or 19 which is specific for a human tumor antigen.

21. The receptor according to claim 20 which is specific for the native human 17-1A antigen.

22. The receptor according to claim 21 wherein said VH chain comprises one of the following two sequences shown in Fig. 7 (nucleotides 1 to 381) and Fig. 8 (nucleotides 1 to 339) and/or said VL chain comprises one of the two following sequences shown in Fig. 6 (nucleotides 1 to 321) and Fig. 9 (nucleotides 1 to 321).

23. A VH chain or ~~a part thereof~~ at least one CDR comprised in the receptor of any one of claims 18 to 22.

24. A VL chain or ~~a part thereof~~ at least one CDR comprised in the receptor of any one of claims 18 to 22.

25. The chain of claim 23 or 24 wherein said ~~part~~ CDR is ~~the~~ CDR3 ~~domain~~

26. A kit comprising a combination of functionally rearranged VH and VL immunoglobulin chains wherein at least one of the VH and VL chains are derived from essentially unprimed mature human B-lymphocytes, ~~or from essentially anergic human B cells,~~ said chains being expressible from recombinant vectors of an in vitro display system.

27. The kit according to claim 26 wherein said in vitro display system is a phage display system.

28. An antibody characterized in that it is derived from human sequences, is specific for the native human 17-1A antigen.

29. The antibody of claim 28 which is low or non-immunogenic in humans.

30. The antibody of claim 28 or 29 which is obtainable according to a method of any one of claims 1 to 17.

31. The antibody of any one of claims 28 to 30 recognizing an epitope of the extracellulary domain of the 17-1A antigen preferably comprising at least one amino acid sequence of peptide Nos. 8, 11, 13, 14, 59, 60, 77 and 79.

32. The antibody of any one of claims 28 to 31, wherein the VH chain comprises at least one CDR of one of the following two sequences shown in Fig. 7 (nucleotides 1 to 381) and Fig. 8 (nucleotides 1 to 339) and/or the VL chain comprises at least one CDR of the following two sequences shown in Fig. 6 (nucleotides 1 to 321) and Fig. 9 (nucleotides 1 to 321).

33. A pharmaceutical composition comprising a receptor of any one of claims 18 to 22, a VH chain of claim 23 or 25, a VL chain of claim 24 or 25 and/or antibody of any one of claims 28 to 32, and optionally a pharmaceutically acceptable carrier.

PA T COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

DEHMEL & BETTENHAUSEN
Müllerstrasse 1
D-80469 München
ALLEMAGNE

Date of mailing (day/month/year)
28 July 1999 (28.07.99)

Applicant's or agent's file reference
C 1567 PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP98/02180

International filing date (day/month/year)
14 April 1998 (14.04.98)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
VOSSIUS & PARTNER
P.O. Box 86 07 67
D-81634 München
Germany

State of Nationality:
State of Residence:
Telephone No.: 089/ 4 13 04-0
Facsimile No.: 089/ 4 13 04-111
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
DEHMEL & BETTENHAUSEN
Müllerstrasse 1
D-80469 München
Germany

State of Nationality:
State of Residence:
Telephone No.: 089/ 23 88 52-6
Facsimile No.: 089/ 23 88 52-70
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
S. De Michiel
Telephone No.: (41-22) 338.83.38

PA IT COOPERATION TREAT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 25 November 1998 (25.11.98)	
International application No. PCT/EP98/02180	**Applicant's or agent's file reference** C 1567 PCT
International filing date (day/month/year) 14 April 1998 (14.04.98)	**Priority date** (day/month/year) 14 April 1997 (14.04.97)
Applicant KUFER, Peter et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

03 November 1998 (03.11.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. De Michiel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

2353328

Copy for the Elected Office (EO/US) PCT/EP98/02180

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

VOSSIUS & PARTNER
P.O. Box 86 07 67
D-81634 München
ALLEMAGNE

Date of mailing (day/month/year) 08 February 1999 (08.02.99)	
Applicant's or agent's file reference C 1567 PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/EP98/02180	**International filing date** (day/month/year) 14 April 1998 (14.04.98)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
MICROMET GESELLSCHAFT FÜR BIOMEDIZINISCHE FORSCHUNG MBH Am Klopferspitz 19 D-82152 Planegg-Martinsried Germany	DE	DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The applicants/inventors have assigned their rights for all designated States except US to the applicant listed in Box 2.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. D Michiel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

002466595

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
C 1567 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 98/02180	14/04/1998	14/04/1997
Applicant		
KUFER, Peter et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [X] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   METHOD FOR THE PRODUCTION OF ANTIHUMAN ANTIGEN RECEPTORS AND USES THEREOF

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/02180

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K16/00 C07K16/30 A61K39/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A. HOESS ET AL.: "Generation of human antibodies that selectively recognize diseased cells overexpressing surface bound antigens." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 38, March 1997, page 30 XP002093904 USA see abstract #198 --- -/--	1-33

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 February 1999	05/03/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Nooij, F

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	M. DUENAS ET AL.: "In vitro immunization of naive human B cells yields high affinity immunoglobulin G antibodies as illustrated by phage display." IMMUNOLOGY, vol. 89, no. 1, September 1996, pages 1-7, XP002093905 Oxford, GB see the whole document ---	1-33
A	A. KREBBER ET AL.: "Reliable cloning of functional antibody variable domains from hybridomas and spleen cell repertoire emplying a reengineered phage display system." JOURNAL OF IMMUNOLOGICAL METHODS, vol. 201, no. 1, 14 February 1997, pages 35-55, XP002093906 Amsterdam, The Netherlands see the whole document ---	1-33
A	A. CATON ET AL.: "Identical D region sequences expressed by murine monoclonal antibodies specific for a human tumor-associated antigen." THE JOURNAL OF IMMUNOLOGY, vol. 144, no. 5, 1990, pages 1965-1968, XP002093907 Baltimore, MD, USA see the whole document ---	1-33
A	H. GÖTTLINGER ET AL.: "The epithelial cell surface antigen 17-1A, a target for antibody-mediated tumor therapy: its biochemical nature, tissue distribution and recognition by different monoclonal antibodies." INTERNATIONAL JOURNAL OF CANCER, vol. 38, no. 1, 15 July 1986, pages 47-53, XP002093908 New York, NY, USA cited in the application see abstract -----	1-33